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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/530,875	04/11/2005	Hans-Georg Kreysch	MERCK-2989	2265

23599 7590 07/27/2006

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EXAMINER	
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ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 07/27/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/530,875	KREYSCH, HANS-GEORG	
	Examiner	Art Unit	
	Laura B. Goddard, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-32* is/are pending in the application.

4a) Of the above claim(s) *3,9,11,16 and 17* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-8,10,12-15 and 18-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/29/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The Election filed May 5, 2006 in response to the Office Action of April 6, 2006 is acknowledged. Applicant elected with traverse the species "A(a)" of **a bispecific antibody wherein said second ErbB receptor molecule type is ErbB1 (EGFR), and wherein the bispecific antibody binds to different epitopes located on the same ErbB receptor molecule type.**

2. Applicants argue that no reference was provided and all of the claims involve related subject matter, therefore a search would comprise overlapping subject matter and it would not be an undue burden on the examiner to carry out a search.

The argument has been considered and is not found persuasive because there was no restriction of inventions into groups, hence a reference is not required to show that a "special technical feature" did not define a contribution over the prior art. There were species elections only and each species of bispecific antibody in species election "A" comprised structurally and functionally distinct binding entities, hence, the species of antibodies lack the same corresponding special technical feature.

Each species of antibody comprises structurally distinct binding sites that function to bind to different antigens. A search of one antibody with distinct binding sites would not be coextensive with a search of another antibody comprising different binding sites that functions to bind to different antigens. Each ErbB molecule is structurally and functionally distinct with distinct ligand binding sites and capabilities of initiating different cellular pathways. A search of all of the possible bispecific antibodies of the instant

application would invoke a high burden of search. For these reasons, the species election requirement is deemed to be proper and is therefore made FINAL.

3. **Rejoined species:** It is noted that Applicant failed to respond to the species election requirements in parts B-E, however, Examiner has rejoined the species in "B" of "first antigen binding sites" derived from Mab425 or Mab225, as well as the species in "C-E" of pharmaceutical compositions further comprising a monospecific anti-ErbB antibody or a cytotoxic agent and kits comprising the same, for examination purposes.

4. Claims 1-32 are pending. Claims 3, 9, 11, 16, and 17 are withdrawn from consideration as being drawn to a non-elected species. Claims 1, 2, 4-8, 10, 12-15, 18-32, as drawn to **a bispecific antibody or fragment thereof having the capability to bind different epitopes located on ErbB1 (EGFR) and a pharmaceutical composition and kits comprising the same,** are currently under prosecution.

Specification

5. The specification is objected to for the following reason: The specification on page 1 should be amended to reflect the most current priority status of the present application, including foreign priority. For example this application is a 371 of PCT/EP03/11165 filed 10/09/2003 and claims priority to foreign applications EPO 02022389.7 filed 10/10/2002 and EPO 02022390.5 filed 10/10/2002.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claim 32 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 32 provides for the "**use of**" a bispecific antibody or a pharmaceutical composition/ kits as defined in claim 1 for the manufacture of a medicament, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

7. Claim 32 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 32 recites "Use of a bispecific antibody or a pharmaceutical composition/ kits **as defined in claim 1**". There is no pharmaceutical composition or kit defined in claim 1. Appropriate correction is required.

8. Claim 19 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claim recites "**biologically effective protein,**

polypeptide or peptide". It is unclear what a biologically effective protein, polypeptide or peptide is and what it biologically affects. Appropriate correction is required.

9. Claims 21 and 28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims recite "**an immunoconjugate as specified in claim 1**". There is no immunoconjugate specified in claim 1. Appropriate correction is required.

10. Claim 24 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claim recites "**a pharmaceutical composition according to claim 1**". There is no pharmaceutical composition in claim 1. Appropriate correction is required.

11. Claim 23 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 23 is indefinite in the use of the expression in parenthesis "(Herceptin)" in that it is not clear whether this recitation is intended to be part of the claim or not. Additionally, it is not clear if Mab 4D5 and Herceptin are one in the same. For example, Herceptin is monospecific to an epitope on HER2 and

manufactured by Genentech that may comprise diluent or other chemicals, whereas "Mab 4D5" may describe a genus of monospecific antibodies that bind to HER2.

Claim 23 contains the trademark/trade name of "Herceptin®". Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark/trade name is used to identify/describe two specific drugs and a specific cream, accordingly, the identification/description is indefinite, MPEP 706.03(d).

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. The specification is objected to AND claims 12-15, 23, and 29 are rejected under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention and failing to provide an enabling disclosure, because the specification does not provide evidence that the claimed biological materials are (1) known and

readily available to the public; (2) reproducible from a written description (e.g. sequenced); or (3) deposited.

The claims are drawn to a bispecific antibody "BAb<h425,c225>" wherein the antigen binding sites are derived from humanized, chimeric, or murine Mab425 and humanized, chimeric, or murine Mab225 (claims 12-15, 23, 29). Claim 23 is also drawn to Mab4D5 or Herceptin®.

It is unclear if the humanized, chimeric, or murine Mab425, humanized, chimeric, or murine MAb225 and MAb4D5 or Herceptin® are known and publicly available, or can be reproducibly isolated without undue experimentation. Clearly, without access to the humanized, chimeric, or murine versions of Mab425 and Mab225 and Mab4D5 or Herceptin®, it would not be possible to practice the claimed invention. Therefore, suitable deposits for patent purposes are required. Without a publicly available deposit of the above cell line, one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed. Although the specification discloses references and product names for some of the preferred antibodies (p. 20, lines 5-10), it is unclear if these antibodies are publicly available or if their structural sequences are disclosed. Exact replication of the claimed antibody's amino acid or nucleic acid sequence is an unpredictable event.

Furthermore, any future amendment to the specification that discloses said monoclonal antibodies (i.e. specifically deposited hybridomas) must make sure that all of the conditions of 37 CFR sections 1.801 through 1.809 have been met. If the deposits were made under the provisions of the Budapest Treaty, filing of an affidavit or

declaration by applicants, assignees or a statement by an attorney of record over his or her signature and registration number stating that the deposits have been accepted by an International Depository Authority under the provisions of the Budapest Treaty, that all restrictions upon public access to the deposits will be irrevocably removed upon the grant of a patent on this application and that the deposit will be replaced if viable samples cannot be dispensed by the depository **is required**. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves these specific matters to the discretion of each State. **Additionally, amendment of the specification to recite the date of the deposit and the complete name and address of the depository is required.**

In view of the above, it would require undue experimentation to reproduce the claimed antibodies necessary for the claimed bispecific antibody and pharmaceutical composition.

13. Claims 1, 2, 4-8, 10, 12-15, and 18-32 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a WRITTEN DESCRIPTION rejection.

The claims are drawn to a bispecific antibody or fragment thereof having the capability to bind to **different epitopes** located on the same **ErbB receptor molecule**

types, said antibody comprising a first antigen-binding site that binds to **an epitope of** a first receptor type, which is ErbB1, and a second different antigen-binding site that binds to **a different epitope** of a second ErbB receptor molecule type (claim 1), wherein said second ErbB receptor molecule type is ErbB1 (EGFR) (claim 2), wherein at least one of said **epitopes is located within the receptor binding domain** (claim 4), wherein said receptor binding domain is **the binding domain of the natural ligand(s)** of said ErbB receptor (claim 5), wherein the first *or* second antigen binding site binds to **an epitope within the binding domain of the natural ligand**(s) of said ErbB receptor molecule type (claim 6), wherein the first *and* second antigen binding site binds to **an epitope within the binding domain of the natural ligand(s)** of said receptor molecule type (claim 7), wherein the antigen binding sites bind to **different epitopes** which are located on the same ErbB receptor molecule type (claim 8), a bispecific antibody of claim 8 wherein the first and second antigen binding site binds to **a different epitope within the binding domain of the natural ligand** of said ErbB receptor, thus blocking an/or inhibiting the receptor, whereby blocking and/or inhibiting the ErbB receptor and induction of down-regulation of ErbB receptor pathway signaling is enhanced as compared with the respective monospecific antibody (claim 10), a bispecific antibody according to claim 1 wherein the first antigen binding site **derives from humanized, chimeric, or murine** MAb 425 (claim 12), a bispecific antibody according to claim 1 wherein said first antigen binding site **derives from humanized, chimeric, or murine** MAb225 (claim 13), a bispecific antibody designated as "BAb<425,c225>" wherein said first antigen-binding site **derives from humanized, chimeric or murine** MAb425 and

second antigen-binding site **derives from humanized, chimeric or murine** MAb225, and each antigen binding site binds to **a different epitope** on the ErbB1 receptor (EGFR) molecule (claim 14), wherein said different epitopes are located within **the binding domain of the natural ligand(s)** (claim 15), wherein the bispecific antibody fragment is F(ab')2 (claim 18), an immunoconjugate comprising a bispecific antibody according to claim 1 fused directly or via a linker molecule via its C-terminus to a biologically effective protein (claim 19, 20), a pharmaceutical composition comprising the bispecific antibody (claim 21, 24-27), a pharmaceutical composition further comprising monospecific anti-ErbB antibody **or a functionally effective fragment thereof** (claims 22, 23), a pharmaceutical kit comprising at least a bispecific antibody or an immunoconjugate as specified in claim 1 and a monospecific anti-ErbB antibody **or a functionally effective fragment thereof** (claims 28-31), use of a bispecific antibody as defined in claim 1 (claim 32).

The specification discloses ErbB receptor molecule types include EGFR (ErbB1), ErbB2, ErbB3 and ErbB4 and **any other members of this family to be identified in the future** (p. 18, lines 24-26). The phrase "within the binding domain" referring to the ErbB receptor binding domain includes **locations in close vicinity** of the real binding domain of the respective natural ligand(s) as well as epitopes actually inside the binding domain (p. 19, lines 9-19). The specification only discloses humanized MAb425 as referenced to US Patent 5,558,864, chimeric MAb225 (or CETUXIMAB®) and HERCEPTIN® (p. 20, lines 5-10). The specification discloses that EGFR binds to at least three ligands: EGF, TGFα and amphiregulin (p. 3, lines 20-21). The specification

does not disclose any other epitopes located "within the receptor binding domain" of EGFR, epitopes "within the binding domain" of the natural ligand(s), binding sites "derived from" humanized, chimeric, or murine MAb425 and MAb225, functionally effective fragments of any antibodies, or any other ErbB receptor molecule types as broadly encompassed in the claims.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claims are a recitation of "epitope located within the receptor binding domain of EGFR", "epitope within the binding domain of the natural ligand(s)", "binding site derived from humanized, chimeric, or murine MAb425", "binding site derived from humanized, chimeric, or murine MAb225", "functionally effective fragment", "blocking an/or inhibiting the receptor", "signaling is enhanced as compared with the respective monospecific antibody", and "ErbB receptor molecule types". Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Although drawn to DNA arts, the findings in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. are relevant to the instant claims. The Federal Circuit addressed the

application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that " [a] written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name', of the claimed subject matter sufficient to distinguish it from other materials. " Id. At 1567, 43 USPQ2d at 1405. The court also stated that:

> a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA" without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.

Id. At 1568, 43 USPQ2d at 1406. The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id.

Finally, the court addressed the manner by which a genus of cDNAs might be described. "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." Id.

The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See Enzo Biochem, Inc. V. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that "the written description requirement can be met by show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ....i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics." Id. At 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

The inventions at issue in Lilly and Enzo were DNA constructs per se, the holdings of those cases are also applicable to claims such as those at issue here. Thus, the instant specification may provide an adequate written description of epitopes located within the receptor binding domain of EGFR, epitopes within the binding domain of the natural ligand(s), binding sites derived from humanized, chimeric, or murine MAb425 and MAb225, functionally effective fragments of any antibodies, or ErbB receptor molecule types, per Lilly by structurally describing representative epitopes located within the receptor binding domain of EGFR, epitopes within the binding domain of the natural ligand(s), binding sites derived from humanized, chimeric, or murine MAb425 and MAb225, functionally effective fragments of any antibodies, or ErbB receptor molecule types or by describing "structural features common to the members of the genus, which features constitute a substantial portion of the genus." Alternatively, per Enzo, the

specification can show that the claimed invention is complete "by disclosure of sufficiently detailed, relevant identifying characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics."

In this case, the specification does not directly describe epitopes located within the receptor binding domain of EGFR, epitopes within the binding domain of the natural ligand(s), binding sites derived from humanized, chimeric, or murine MAb425 and MAb225, functionally effective fragments of any antibodies, or ErbB receptor molecule types useful in the claimed invention in a manner that satisfies either the Lilly or Enzo standards. Although the specification discloses that ErbB receptor molecule types include EGFR (ErbB1), ErbB2, ErbB3 and ErbB4, and discloses the antibodies humanized MAb425, as referenced to US Patent 5,558,864, chimeric MAb225 (or CETUXIMAB®) and HERCEPTIN® (p. 20, lines 5-10), this does not provide a description of the broadly claimed epitopes located within the receptor binding domain of EGFR, epitopes within the binding domain of the natural ligand(s), binding sites derived from humanized, chimeric, or murine MAb425 and MAb225, functionally effective fragments of any antibodies, or ErbB receptor molecule types that would satisfy the standard set out in Enzo because the specification provides no functional characteristics coupled to structural features.

Further, the specification also fails to describe epitopes located within the receptor binding domain of EGFR, epitopes within the binding domain of the natural ligand(s), binding sites derived from humanized, chimeric, or murine MAb425 and

MAb225, functionally effective fragments of any antibodies, or ErbB receptor molecule types by the test set out in Lilly because the specification describes only ErbB receptor molecule types: EGFR (ErbB1), ErbB2, ErbB3 and ErbB4, and the antibodies: humanized MAb425, as referenced to US Patent 5,558,864, chimeric MAb225 (or CETUXIMAB®) and HERCEPTIN®. Therefore it necessarily fails to describe a representative number of such species.

Thus, the specification does not provide an adequate written description of a epitopes located within the receptor binding domain of EGFR, epitopes within the binding domain of the natural ligand(s), binding sites derived from humanized, chimeric, or murine MAb425 and MAb225, functionally effective fragments of any antibodies, or ErbB receptor molecule types that is required to practice the claimed invention.

Further, the following teaching of the court as set out in Noelle also clearly applies to the instant claimed invention. The court teaches as follows: "Noelle did not provide sufficient support for the claims to the human CD40CR antibody in his '480 application because Noelle failed to disclose the structural elements of human CD40CR antibody or antigen in his earlier '799 application. Noelle argues that because antibodies are defined by their binding affinity to antigens, not their physical structure, he sufficiently described human CD40CR antibody by stating that it binds to human CD40CR antigen. Noelle cites Enzo Biochem II for this proposition. This argument fails, however, because Noelle did not sufficiently describe the human CD40CR antigen at the time of the filing of the '799 patent application. In fact, Noelle only described the mouse antigen when he claimed the mouse, human, and genus forms of CD40CR

antibodies by citing to the ATCC number of the hybridoma secreting the mouse CD40CR antibody. If Noelle had sufficiently described the human form of CD40CR antigen, he could have claimed its antibody by simply stating its binding affinity for the "fully characterized" antigen. Noelle did not describe human CD40CR antigen. Therefore, Noelle attempted to define an unknown by its binding affinity to another unknown. As a result, Noelle's claims to human forms of CD40CR antibody found in his '480 application cannot gain the benefit of the earlier filing date of his '799 patent application. Moreover, Noelle cannot claim the genus form of CD40CR antibody by simply describing mouse CD40CR antigen". *Randolph J. Noelle v Seth Lederman, Leonard Chess and Michael J. Yellin* (CAFC, 02-1187, 1/20/2004).

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

14. Claim 32 is rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

15. Claims 1, 2, 4-8, 13, 18-21, and 24-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fan et al (Cancer Research, 1993, 53:4322-4328) in view of Robert et al (Int J Cancer, 1999, 81:285-291) and Zhu (US Patent Application 2002/0103345 A1, filed 5/24/2001, published 8/1/2002).

The claims are drawn to a bispecific antibody or fragment thereof having the capability to bind to different epitopes located on the same ErbB receptor molecule types, said antibody comprising a first antigen-binding site that binds to an epitope of a first receptor type, which is ErbB1, and a second different antigen-binding site that binds to a different epitope of a second ErbB receptor molecule type (claim 1), wherein said second ErbB receptor molecule type is ErbB1 (EGFR) (claim 2), wherein at least one of said epitopes is located within the receptor binding domain (claim 4), wherein said receptor binding domain is the binding domain of the natural ligand(s) of said ErbB receptor (claim 5), wherein the first *or* second antigen binding site binds to an epitope within the binding domain of the natural ligand(s) of said ErbB receptor molecule type (claim 6), wherein the first *and* second antigen binding site binds to an epitope within the binding domain of the natural ligand(s) of said receptor molecule type (claim 7), wherein the antigen binding sites bind to different epitopes which are located on the

same ErbB receptor molecule type (claim 8), wherein said first antigen binding site derives from humanized, chimeric, or murine Mab225 (claim 13), wherein the bispecific antibody fragment is F(ab')2 (claim 18), an immunoconjugate comprising a bispecific antibody according to claim 1 fused directly or via a linker molecule via its C-terminus to a biologically effective protein (claim 19), wherein the protein is a cytokine (claim 20), a pharmaceutical composition comprising a bispecific antibody optionally together with a pharmaceutically acceptable carrier, diluent or excipient (claim 21), a pharmaceutical composition according to claim 1 additionally comprising a cytotoxic agent (claim 24), wherein said cytotoxic agent is a chemotherapeutic agent (claim 25), wherein said chemotherapeutic agent is selected from cisplatin, doxorubicin (claim 26), and wherein said cytotoxic agent is a cytokine (claim 27).

Fan et al teach bivalent antibodies, Mab225 and Mab528, which bind to EGFR and inhibit binding of EGFR to its natural ligands, prevent ligand-induced activation of EGFR tyrosine phosphorylation, and inhibit proliferation of cells expressing EGFR and its ligands, such as breast cancer cells (p. 4322, col. 2). Fan et al teach attempting to block the function of receptors for growth factors as an approach to cancer therapy and that they are using anti-EGFR antibodies, such as Mab225, as a pharmaceutical in a clinical setting for therapy of patients with malignancies expressing high levels of EGFR (p. 4322, col. 2). Fan et al teach that the F(ab')2 fragment of Mab225 could inhibit ligand binding and signaling of ligands to EGFR, however, it could not inhibit cell proliferation as effectively as bivalent Mab225, had reduced binding affinity to EGFR, and a shorter half-life. Fan et al teach suggest that extremely large amounts of F(ab')2 fragment

would have to be continuously infused in order to obtain stable plasma concentrations which could saturate EGFR. Fan et al conclude that EGFR blockade may be useful in antitumor therapy and that the demonstration of *in vivo* activity of bivalent Mab225 F(ab')2 fragment establishes that Mab225 can act as a pharmacological EGFR blocking agent. Fan et al suggests using a murine/human chimeric antibody for therapy in future trials (abstract; p. 4327, cols. 1-2). Fan et al does not teach a bispecific antibody having the capability to bind to *different* epitopes located on the same EGFR receptor molecule type.

Robert et al teach a bispecific antibody having the capability to bind to different epitopes located on carcinoembryonic antigen (CEA), wherein the epitopes do not overlap with each other. Robert et al teach the advantage of bispecific binding over conventional F(ab')2 binding and demonstrate that bispecific antibodies binding to different epitopes on the same molecule had higher tumor uptake than that of parental F(ab')2 (abstract). Robert et al teach that the bispecific antibodies have increased affinity/ avidity/ and tumor retention time, particularly if the antibodies bind to epitopes that are close together (abstract; p. 285, col. 2; p. 290, col. 2).

Zhu teaches the production of bispecific antibodies that have a binding domain specific for one epitope and a binding domain specific for a second epitope on the same antigen (abstract), wherein the antibodies are used to block an interaction of a protein and its ligand ([0030]), wherein the antibodies bind to EGFR and neutralize activation of the receptor ([0062]), and wherein the antibody is C225 (chimeric MAb225), a chimeric IgG1 antibody directed against EGFR ([0099]). Zhu teach several advantages of

bispecific antibodies, one of which is that the bispecific antibodies allow for cooperation of binding and a significant increase in binding avidity over an antibody comprising a single antigen-binding site ([0023]). Zhu teaches that bispecific antibodies can be biosynthetically or chemically linked using conventional methods to anti-tumor agents including cytokines and chemotherapeutic agents known to those skilled in the art including cisplatin and doxorubicin ([0079], [0082]).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute the anti-EGFR mAb225 and mAb528 or F(ab')2 fragments of the antibodies taught by Fan et al into the bispecific antibodies taught by Robert et al and Zhu because Robert et al and Zhu teach bispecific antibodies that bind to different epitopes on the same molecule, including binding to EGFR. One would have been motivated to substitute the anti-EGFR mAb225 and mAb528 taught by Fan et al into the bispecific antibodies taught by Robert et al and Zhu in order to increase binding avidity over an antibody comprising a single antigen-binding site, increase tumor targeting to tumors expressing EGFR, and increase tumor retention time for therapy of patients with malignancies that express EGFR. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to make an immunoconjugate of the antibody taught by the combined references because Zhu teach that attaching anti-tumor agents to antibodies is conventional and teaches chemotherapeutics and cytokines well-known in the art used for immunoconjugates. Attaching a moiety to the C-terminus of an antibody is well within the level of one of ordinary skill in the art and is a conventional method of attachment. One would have

been motivated to make an immunoconjugate of the bispecific antibody taught by the combined references in order to increase tumor targeting of the anti-tumor or cytotoxic agents for therapeutic treatment of malignancies expressing EGFR. One of ordinary skill in the art would have a reasonable expectation of success of making the bispecific antibody of the combined references because the antibodies binding to EGFR ligand binding domains and blocking EGFR signaling were known in the art as well as the technology for making bispecific antibodies and immunoconjugates.

16. Claims 22 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fan et al (Cancer Research, 1993, 53:4322-4328), Robert et al (Int J Cancer, 1999, 81:285-291) and Zhu (US Patent Application 2002/0103345 A1, filed 5/24/2001, published 8/1/2002), in view of Albanell et al (Drugs Today, 1999, 35:931-946) and Kim et al (Experimental Cell Research, 1999, 253:78-87).

The claims are drawn to a pharmaceutical composition of claim 21 further comprising a monospecific anti-ErbB antibody (claim 22), wherein said monospecific anti-ErbB antibody is Mab 4D5 (claim 23).

Fan et al, Robert et al, and Zhu teach a pharmaceutical composition comprising a bispecific antibody or immunoconjugate having the capability to bind to different epitopes located on the same EGFR receptor molecule type as set forth above. The combined references do not teach the pharmaceutical composition further comprising antibody MAb 4D5.

Albanell et al teach that monoclonal MAb4D5 binds to HER2 (ErbB2) and a recombinant humanized MAb4D5 is used to treat patients with breast cancer. Chemotherapeutics, such as doxorubicin or paclitaxel, are used in addition to MAb4D5 to treat patients, wherein a clinical trial demonstrated that administration of MAb4D5 in addition to chemotherapy enhanced the effects of chemotherapy on time to disease progression, response rates, and survival (abstract).

Kim et al teach that EGFR and HER2 are expressed in breast cancer. HER2 is the substrate of activated EGFR following stimulation of EGFR with its ligands EGF or TGFα (p. 78, col. 2). Kim et al teach that EGFR and HER2 are strongly implicated in the development and progression of human cancers (p. 78, col. 1).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to add Mab4D5 and/or cytotoxic agents such as chemotherapeutics to the pharmaceutical composition comprising the bispecific antibody taught by the combined references because Mab4D5 and chemotherapeutic agents are known to treat breast cancer which also expresses EGFR. One of ordinary skill in the art would have been motivated to combine Mab4D5 and or chemotherapeutic agents with the bispecific antibody pharmaceutical taught by the combined references in order to treat breast cancer using the combination of agents that inhibit breast cancer growth via different receptors or mechanisms. Each of these agents had been taught by the prior art to be effective in inhibiting the growth of breast cancer cells, thus the instant situation is amenable to the type of analysis set forth in In re Kerkhoven, 205 USPQ 1069 (CCPA 1980) wherein the court held that it is *prima facie* obvious to combine

modes of treatment, each of which is taught by the prior art to be useful for the same purpose in order to make a protocol that is to be used for the very same purpose since the idea of combining them flows logically from their having been individually taught in the prior art. Applying the same logic to the instant composition claims, given the teaching of the prior art of using either Mab225, Mab528, Mab4D5 and chemotherapeutics in the method of inhibiting breast cancer cell growth, it would have been obvious to combine the agents in a pharmaceutical because the idea of doing so would have logically followed from their having been individually taught in the prior art to be useful as agents for the same purpose of inhibiting breast cancer cell growth.

17. Claims 28, 30, and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fan et al (Cancer Research, 1993, 53:4322-4328), Robert et al (Int J Cancer, 1999, 81:285-291), Zhu (US Patent Application 2002/0103345 A1, filed 5/24/2001, published 8/1/2002), Albanell et al (Drugs Today, 1999, 35:931-946), and Kim et al (Experimental Cell Research, 1999, 253:78-87), in further view of Stratagene Catalog 1988, p. 39.

The claims are drawn to a pharmaceutical kit comprising a first package comprising at least a bispecific antibody or an immunoconjugate as specified in claim 1 and a second package comprising at least a monospecific anti-ErbB antibody (claim 28), comprising additionally a third package comprising a cytotoxic drug (claim 30), and wherein the cytotoxic drug is doxorubicin or paclitaxel (claim 31).

Fan et al, Robert et al, Zhu, Kim et al and Albanell et al teach a pharmaceutical composition comprising a bispecific antibody capable of binding to two different epitopes on ErbB1 further comprising Mab4D5 and a chemotherapeutic such as doxorubicin or paclitaxel as set forth above.

Stratagene catalog teaches a motivation to combine agents into kit format (page 39).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine the agents of the combined references into a kit format as discussed by Stratagene catalog since the Stratagene catalog teaches a motivation for combining reagents of use into a kit, "Each kit provides two services: 1) a variety of different reagents have been assembled and pre-mixed specifically for a defined set of experiments. Thus one need not purchase gram quantities of 10 different reagents, each of which is needed in only microgram amounts, when beginning a series of experiments. When one considers all of the unused chemicals that typically accumulate in weighing rooms, desiccators, and freezers, one quickly realizes that it is actually far more expensive for a small number of users to prepare most buffer solutions from the basic reagents. Stratagene provides only the quantities you will actually need, premixed and tested. In actuality, the kit format saves money and resources for everyone by dramatically reducing waste. 2) The other service provided in a kit is quality control" (page 39, column 1). One would have been motivated to form a kit comprising the agents taught by the combined references in order to provide a pre-measured, quality controlled product for therapy of breast cancer in patients.

18. **Conclusion:** No claims are allowed.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Laura B. Goddard, Ph.D. whose telephone number is (571) 272-8788. The examiner can normally be reached on 8:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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